

## METHOD FOR THE TREATMENT OF ACNE

## Field of the Invention

This invention relates to methods for the treatment of acne, and in particular to methods for the treatment of acne involving the use of oral tetracycline antibiotics.

## Background of the Invention

Oral tetracycline antibiotics are frequently used in the treatment of acne. One of the most effective oral tetracycline antibiotics used in the treatment of acne is minocycline. All tetracycline antibiotics are known to have some side effects. These side effects include vestibular symptoms such as vertigo, dizziness or blurred vision. These effects are sometimes disabling. See, Gould & Brookler, Arch. Otolaryng. Vol. 96, p. 291 (1972); Williams et al., Lancet, Sept. 28, 1974, p. 144-45; Fanning & Gump, Arch. Intern. Med., Vol. 136, pp. 761-62 (1976). Headache and general malaise, along with gastro-intestinal symptoms such as the diarrhea, nausea, gas, or cramps also occur. Dry nose and dry mouth are also occasionally encountered.

Dosage forms of oral tetracycline antibiotics are typically constructed with a view towards achieving rapid dissolution rates. Rapid dissolution is believed to be essential to the effectiveness of these drugs. The driving force behind this practice is the understanding that rapid dissolution leads to rapid assimilation through the gut lining, where the antibiotics are then transmitted through the blood stream to the skin, where they are active against bacteria associated with acne. The United States Food and Drug Administration (FDA) has established standards for dissolution rates for various oral antibiotics. These standards set minimum

dissolution rates. For example, the FDA standard for oral minocycline is that 75 percent of the stated dosage must have dissolved within 45 minutes, under standard U.S. Pharmacopeia test conditions. Commercial products are typically engineered to have a dissolution rates which are substantially faster than that required by the FDA. All of this is based upon the generally accepted belief in the art that, while dissolution rates enhance the effectiveness of the antibiotic, once the FDA minimum dissolution rate is achieved, all products have equivalent safety and efficacy.

### Summary of the Invention

It has been discovered that the dissolution rate of oral tetracycline antibiotics, especially minocycline, can affect the occurrence of vestibular side effects. Specifically, too rapid dissolution of oral tetracyclines increases the incidence and severity of vestibular side effects. By reducing or slowing the dissolution rates of the antibiotics, the incidence and/or severity of vestibular side effects can be reduced significantly.

### Detailed Description of the Invention

Vestibular reactions are an undesirable and sometimes seriously disconcerting side effect of minocycline therapy. According to the present invention, it is possible to provide persons susceptible to such side effects with the benefits of minocycline therapy while diminishing the incidence and/or severity of these side effects. This is accomplished by adjusting the dissolution rate of the minocycline in its dosage form so that, while an effective concentration of minocycline is achieved in the blood stream of the patient, vestibular side effects are greatly reduced.

Minocycline is available from a variety of sources. Various commercial products containing minocycline as their active ingredient have a variety of the dissolution rates. In the following example, slower dissolving minocycline is compared with fast-dissolving minocycline.

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kilograms, 200 milligrams. This dose was given once a day at 5 p.m.. Subjects received one of the two dose forms for four days. After a two week washout, each group "crossed over" and received the dosage form that they had not received during the first four day period. Each subject was required to maintain an accurate diary of vestibular side effects. The diary recorded the number of days that each subject experienced vestibular side effects and the number of incidents of each symptom. The 32 subjects were evaluated over a five day period, yielding 160 person-day measurements per treatment group. The number of days that each subject recorded a side effect and the severity of that side effect the reported in Table 1.

From Table 1 it can be seen that a total of 27 incidents of vestibular side effects occurred in the fast dissolving treatment group, compared to only five incidents in the slower dissolving group. The severity of the vestibular side effects are reported on a scale of 1 to 4. With 1 indicating slight severity, 2 indicating mild severity, 3 moderate, and 4 severe side effects.

The dissolution rates for the fast dissolving dosage form and the slower dissolving dosage form are set forth below.

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**Table 1**

**Vestibular Side Effects**

**Patients Treated With Slower-Dissolving Minocycline**

<b>Symptom</b>	<b>Severity</b>	<b>No. of Time Intervals</b>	<b>Duration</b>	<b>Severity Category</b>
dizziness	slight	2	8:00 am-4:00 pm	1
dizziness	slight-mild	4	all day	1.5
dizziness	mild	1	on and off	2
dizziness	slight	1	all evening	1
dizziness	slight-mild	2	morning thru mid day	1.5

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**Table 1 (contd.)**

**Patients Treated With Fast-Dissolving Minocycline**

<b>Symptom</b>	<b>Severity</b>	<b>No. of Time Intervals</b>	<b>Duration</b>	<b>Severity Category</b>
dizziness	slight	2	7:00 am-12:00 pm	1
blurred vision	slight-mild	2	8:00 am-3:00 pm	1.5
dizziness	slight	2	7:00 am-12:00 pm	1
dizziness	slight	2	8:00 am-2:00 pm	1
dizziness	slight	2	7:00 am-2:00 pm	1
dizziness	slight	2	7:00 am-3:00 pm	1
dizziness	slight	2	morning-late afternoon	1
dizziness	slight	2	morning-late afternoon	1
dizziness	slight	2	morning-late afternoon	1
dizziness	slight	1	1 hour	1
dizziness	slight	1	2 hours	1
dizziness	slight	1	about 1-2 hours	1
dizziness	slight	1	about 1.5 hours	1
dizziness	slight	1	2 hours	1
blurred vision	slight	1	1 hour	1
dizziness	slight	1	2 hours	1
dizziness	slight-mild	2	7.5 hours	1.5
dizziness	mild	1	6:00 am-8:00 am	2
vertigo	mild	1	2:00 am-8:00 am	2
dizziness	mild	1	6:00 am-8:00 am	2
vertigo	mild	1	2:00 am-8:00 am	2
dizziness	mild	1	6:00 am-8:00 am	2
vertigo	mild	1	6:00 am-8:00 am	2
dizziness	mild	1	6:00 am-8:00 am	2
vertigo	mild	1	6:00 am-8:00 am	2
dizziness	mild	1	6:00 am-8:00 am	2
vertigo	mild	1	6:00 am-8:00 am	2

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**Table 2**

<b>Fast Dissolving</b>		<b>Slow Dissolving</b>	
<b>Time (Min.)</b>	<b>% Dissolution</b>	<b>Time (Min.)</b>	<b>% Dissolution</b>
0	0.0	0	0.0
15	100	15	30
30	100	30	67
45	100	45	88
60	100	60	95

The cause of the effectiveness of this invention is not known. However, it can be

speculated that the dissolution rates called for by the present invention allow the vestibular organs to acclimate themselves to the presence of the minocycline, and thereby avoid unwanted side effects. This explanation is consistent with the avoidance of vestibular side effects even though the use of both slow and fast dissolving dosage forms may achieve the same level of minocycline in the blood stream.

The foregoing example is given by way of illustration only. The scope of the invention is defined only by the following claims.